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Enabling Darwinian evolution in chemical replicators

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CONCLUSIONS AND PERSPECTIVES

Through the work carried out in this thesis, a better understanding of molecular evolution has been achieved. Three main areas have been explored and advanced: exponential replication as an evolutionary advantage, replication under far-from-equilibrium conditions to enable growth in a regime of dynamic kinetic stability (as opposed to inertness) and ultimately evolution, and propagation of sequence in the replication process as an information transfer mechanism that defines which characteristics are passed on to further generations.

Firstly, the exponential nature of the replication process in our peptide based system has been determined and confirmed, as described in *Chapter 2*. Such a finding represents a breakthrough in current research, as exponential replication resulting from removing the hindrance of duplex pairing eventually leads to unique enhanced competitiveness, an important evolutionary trait of a chemical replicator. After these findings, further research efforts should extend the scope of the results to other sequences and further relate exponential replication to the evolutionary properties of the systems, i.e., survival of the best replicator. Furthermore, seeking well-defined conditions to achieve parabolic and hyperbolic replication (i.e., sub-exponential and super-exponential replication, respectively) would constitute another important future goal, as other replication orders correspond to peculiar evolutionary properties of the corresponding replicators.

Secondly, a far-from-equilibrium version of the replicative system has been setup and studied, as shown in *Chapter 3*. This system is based on the unique potential of our dynamic combinatorial system to undergo induced reduction and oxidation at the disulfide bridges. These processes have been studied and verified independently. Computational tools to better understand the dynamics of the system have also been set up and have helped to assess the key parameters needed to impose efficient recycling conditions in the system and to fine tune the rates of key processes, i.e., replication, destruction, quenching, and exchange. The development of a far-from-equilibrium replication platform constitutes a major step forward towards molecular evolution in the laboratory.

The next step in this research area involves fully understanding the implications of far-from-equilibrium conditions in a replicating system, by two means: developing a theoretical model and making use of computer simulations involving multiple building blocks. Once evolutionary scenarios in far-from-equilibrium conditions, which might involve phase transitions between states of different stabilities (in DKS terms), have been explored, reproducing them in the laboratory would be the next clear research goal.

In the big picture, the pathway to further progress will very likely involve building far-from-equilibrium conditions into new supramolecular systems, by allowing them to continuously dissipate energy. As illustrated by the examples outlined in Chapters 1 and 3, such systems require species that are being formed and degraded continuously, but along pathways that are separate, chemically distinct, hence not each other's microscopic reverse. The simplest possible scenario is a reaction-diffusion system, in which diffusion takes care of the destruction pathway. More advanced systems would be based on destruction through a (photo)chemical reaction and/or a supramolecular process. The currently most easily accessible of such systems are photoisomerization processes in which the system relaxes through a thermal back reaction that is chemically distinct from the photochemical forward reaction. Only very few examples, among which our replicating system, have been reported of systems in which the formation and destruction pathways are both chemical (as opposed to photochemical) reactions. Given the wealth of reactions in organic chemistry there must be many more processes possible in which formation and destruction occur continuously in a single system, mediated (and therefore fuelled) by separate reagents. The current scarcity of such systems in the literature (at least explicitly) represents a bottleneck for further developments in the area of far-from-equilibrium systems chemistry. This bottleneck is probably more due to a lack of serious efforts in searching for suitable reaction pairs, rather than to any fundamental difficulty. We invite the organic chemists to join us in developing new chemical formation-destruction systems, both by studying already known systems under such conditions and by designing new formation-destruction reaction pairs, as these will be the workhorses for the far-from-equilibrium chemical systems of the future.

Finally, mechanistic insights have been gathered regarding the pathway complexity of fibre elongation, breakage, and destruction, as illustrated in *Chapter 4*. The detailed process the system follows clarifies how information, in the form of sequential structure of peptides along a fibre, might have been propagated or prevented from propagating in early replicating systems.

Pathway complexity research is thriving and given the relative straightforwardness of the necessary experiments in our specific system, many possibilities can be envisioned to further investigate propagation and loss of information during replication and exchange. Detailed experiments could be carried out in order to determine relative replication strengths (as relative rates of replication) of different peptide systems and to investigate ways to block the fastest replicators within a long fibre, thereby suppressing its evolutionary advantage and preventing it from turning available building blocks into more copies of itself. The opposite effect could also be studied, namely the introduction of additional sequences in the building block pool via fibre breakage and the consequences on the replicator space.

Our findings on exponential growth, far-from-equilibrium replication, and information transfer represent an important milestone for studies on molecular Darwinian evolution.